this rejection and the vacated restriction appear to be that the Office has treated each of the specific peptide sequences appearing in a dependent claim as a separate group, not as individual species of a genus. The present restriction requirement sets forth the following groups of claims:

I. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:1, classified in Class 424, subclass 85.6.

II. Claims 1-16, 21, 22, 25-37, 42, 43, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:2, classified in Class 424, subclass 85.6.

III. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:3, classified in Class 424, subclass 85.6.

IV. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:4, classified in Class 424, subclass 85.6.

V. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:5, classified in Class 424, subclass 85.6.

VI. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:6, classified in Class 424, subclass 85.6.

VII. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:7, classified in Class 424, subclass 85.6.

VIII. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:8, classified in Class 424, subclass 85.6.

IX. Claims 1-16, 21, 25-37, 42, 44, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:9, classified in Class 424, subclass 85.6.

X. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:10, classified in Class 424, subclass 85.6.

XI. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:11, classified in Class 424, subclass 85.6.

XII. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:12, classified in Class 424, subclass 85.6.

XIII. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:13, classified in Class 424, subclass 85.6.

XIV. Claims 1-16, 21, 25-37, 42, 46-69, drawn to a composition and method using HIV-1 antigen SEQ ID NO:14, classified in Class 424, subclass 85.6.

XV. Claims 1-15, 17, 25-36, 46-65, and 67-69, drawn to influenza antigens, classified in Class 424, subclass 85.6.

XVI. Claims 1-15, 18, 25-36, 39, 46-65, and 67-69, drawn to rotavirus antigens, classified in Class 424, subclass 85.6.

XVII. Claims 1-14, 19, 25-35, 40, 46-65, and 67-69, drawn to pathogenic bacterium or protozoan, classified in Class 424, subclass 85.6.

XVIII. Claims 1-15, 20, 25-35, 41, 46-65 and 67-69, drawn to tumor-associated antigens, classified in Class 424, subclass 85.6.

Although the claims are classified by the Examiner in the same class and subclass, the Examiner has allegedly determined that "the inventions of each of the groups encompass patentably distinct antigens that differ from each other and they are derived from very different sources and would effect different diseases." Further, the Examiner alleges that each peptide sequence is different and is considered to be a separate distinct invention and that the search for each group would not be coextensive with the other groups and that there "would be an undue burden on the Office to search all of these groups."

Applicants elect, with traverse, to prosecute Group II, claims 1-16, 21, 22, 25-27, 42, 43, and 46-69, wherein the claims are drawn to a composition and method using HIV-1 antigen designated SEQ ID NO:2. Applicants reserve the right to file a divisional or related application(s) to the claims of any non-elected group. Further, Applicants respectfully request reconsideration of the request for restriction. In particular, Applicants request the Examiner to consider examining together the claims of Groups I though XIV, or optionally the claims of at least Group I through Group VII. Contrary to the statement of the Examiner the antigens are not derived from very different sources, nor would they effect different diseases. This request for

reconsideration is made in order that Applicants might be allowed a compact and expedited prosecution of the present invention and to provide a patent which adequately protects the entire invention.

Restriction can be required by the Office for certain reasons as set forth in the MPEP under section 800. Restriction of prosecution to certain claimed subject matter is entirely at the discretion of the Office, but this must be balanced against Applicants being allowed to claim their invention in such a full and complete manner to adequately protect their entire invention and to provide for a compact and expedited prosecution. The Office can require restriction for several reasons including the following: (a) so that an undue burden is not placed on the Examiner in prosecuting the application, (b) so that the statutory fee structure is not subverted, and (c) so that the integrity of the examination and classification system of the Office are not jeopardized.

Applicants submit that any burden on the Office in the instant case is outweighed by Applicants loss of their ability to adequately protect their invention in a full and complete manner and their loss of a compact and expedited prosecution. The division of the present invention into separate groups, including fourteen groups comprising structured and functionally related peptides, would require the filing, prosecution and maintenance of fourteen to eighteen separate patents to protect the entire scope of the invention. Applicants submit the presently claimed invention relates to methods, which together comprise a single inventive concept. The peptides encompassed by the claims in at least Groups I through XIV are derived from a similar source, share certain structural characteristics, and are used to effect the same or similar diseases. Applicants do not believe the Examiner has provided sufficient reasoning to support an allegation that a serious burden would be placed on the Office to require the present restriction.

Under 35 U.S.C. § 121, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(1) the inventions must be independent or distinct as claimed; and

(2) there must be a serious burden on the Examiner if restriction is not required. See MPEP § 103.

A serious burden on the Examiner may be *prima facie* shown if the Examiner shows by appropriate explanation separate classification, or separate status in the art, or that the claims are in a different field of search as defined in MPEP § 808.02. The *prima facie* showing can be rebutted by Applicants. Further, the criteria for restriction practice relating to Markush-type claims is not set forth in MPEP § 803.02.

For Markush-type claims, if the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the Examiner must examine all members of the Markush groups in the claims on the merits, even though they are directed to independent and distinct inventions.

Applicants submit that the criteria for restriction have not been met by the Examiner in requiring restriction of the claims in the present application into 18 groups. In particular, claim 21 is a Markush-type claim reciting the peptides used to set forth Groups I-XIV has only 14 elements which are related by both structure and use. The present invention generally relates to the single inventive concept of methods of inducing a protective mucosal cytotoxic T lymphocytes response in a mammalian subject comprising contacting a mucosal tissue of the subject with a composition comprising a soluble antigen. More specifically, the present invention provides a method for inducing a protective mucosal cytotoxic T lymphocyte response using any one or more of a number of distinct soluble polypeptides from a number of sources, including, for example, pathogenic viruses (*i.e.*, HIV, influenza, and rotavirus) as well as polypeptide, from pathologic bacteria or protozoa, or a tumor-associated polypeptide. In particular, the polypeptide comprises a cluster peptide containing cytotoxic T cell epitopes, T helper epitopes and neutralizing epitopes of HIV. (The methods, as claimed, can also comprise the administration of a composition further comprising a cytokine with or without interferon. Because these method claims represent a single invention concept, Applicants believe they properly encompass a single prosecutable invention.

Further, Applicants contend that even should the Examiner consider the request for restriction final, the claims of the invention should not be divided into 18 distinct and separate inventions. Applicants do not believe restriction into such a large number of groups provides for a compact and expedited prosecution of the entire invention concept nor adequately protects the invention as claimed. Also, as set forth in MPEP § 803.02 for Markush-type claims, if the number of members in the claims are sufficiently few or so closely related that a search and examination of the entire claim can be made without serious burden, the claims should be examined together.

Applicants assert that the claims of Groups I through XIV as drawn to a composition and method using HIV-1 antigen of SEQ ID NOs. 1-14 should be examined together. As above, contrary to the statement of the Examiner the polypeptides of SEQ ID NOs. 1-14 share a substantial structural feature disclosed necessary to the claimed utility. Each of the Groups are designated by a polypeptide. These polypeptides are synthetic multi-determinant peptides or cluster peptides that are composed of sub-regions containing epitopes that evoke an antigen specific mucosal cytotoxic T cell response. Further, the polypeptides contain (a) a sub-region with multiple overlapping helper T cell activating epitopes that can be presented by multiple MHC class II molecules (b) a sub-region with a CTL activating epitope, and (c) a sub-region that elicits the production of a neutralizing antibody. The epitopes of a polypeptides designated SEQ ID NOs: 1-14 are all derived from gp160 of HIV. Further, the polypeptides designated SEQ ID NOs.: 1-7 contain the neutralizing epitopic region P18 from HIV-1 isolate IIIB at the carboxy end, while the polypeptides designated SEQ ID NOs: 8-14 contain the related neutralizing epitopic region P18 from HIV-1 isolate MN.

Applicants believe that for the above reasons the claims of Groups I through XIV or at least the claims of Groups I through VII should be examined together as the polypeptides are members of a Markush-type claim and the members are sufficiently few in number or so closely related that a search and examination of the generic claims drawn to the members of the claims (claim 21) can be made without serious burden on the Examiner.

CONCLUSION

In view of the foregoing, Applicants have elected with traverse Group II, claims 1-16, 21, 22, 25-37, 42, 43, and 46-69 drawn to a composition and method using HIV-1 antigen SEQ ID NO:2. Reconsideration of the request for restriction is respectfully requested for the reasons set forth above. Applicants believe all claims now pending in this application, are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If for any reason the Examiner believes that a telephone conference would expedite prosecution of the subject application, the Examiner is invited to telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 23 May 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Kindly replace the paragraph at page 5, line 34 to page 6, line 4, with the following paragraph:

Also provided within the invention are immunogenic compositions for inducing a protective mucosal CTL response in a subject which are adapted for intrarectal administration. The compositions comprise a purified soluble antigen formulated for intrarectal delivery to the rectum, colon, sigmoid colon, or distal colon. They may be formulated as a rectal enema, foam, suppository, or topical gel and generally comprise a base, carrier, or [aabsorption-promoting] absorption-promoting agent adapted for intrarectal delivery.

Kindly replace the paragraph at page 6, lines 23-28, with the following paragraph:

To optimize intrarectal delivery, the immunogenic compositions of the invention also preferably include an absorption-promoting agent, for example a surfactant, mixed micelle, enamine, nitric oxide donor, sodium salicylate, glycerol ester of acetoacetic acid, [clyclodextrin] cyclodextrin or beta-cyclodextrin derivative, or medium-chain fatty acid.

Kindly replace the paragraph at page 9, lines 1-8, with the following paragraph:

Fig. 11 demonstrates that protection induced by mucosal immunization with HIV-1 peptide vaccine is specific. On day 35, mice were challenged intrarectally with 2.5 X 10^7 plaque-forming units (pfu) of vaccinia virus expressing gp [160IIB] 160IIIB (vPE16) or with 2.5 X 10^7 pfu of vaccinia virus expressing β-galactosidase (vSC8). Bars = SEM of five mice per group. The difference is significant at $P< 0.01$ by Student's test.

Kindly replace the paragraph at page 11, lines 10-35, with the following paragraph:

IR immunization induced long-lasting protective immune responses. For example, antigen-specific CTL were found in both mucosal and systemic sites 6 months after

immunization. IR immunization with the antigenic peptide elicited significantly stronger CTL responses than IN immunization with the same peptide. While IR administration with PCLUS3-18IIIB (SEQ ID NO:2) induced a significant response when administered alone, the response was enhanced by the inclusion of CT. The CTL were [CDB+] $\underline{CD8^+}$ T lymphocytes restricted by MHC class I molecules, recognizing MHC class I positive target cells either endogenously expressing *HIV-1* gp160 or pulsed with an appropriate gp160 peptide. Induction of both mucosal and systemic CTL response by IR immunization was IL-12-dependent, as shown by inhibition of induction of CTL in mice treated i.p. with anti-IL-12 antibody. Furthermore, inclusion of IL-12 in the composition of antigenic peptide and CT used for IR immunization resulted in enhanced mucosal and systemic CTL responses relative to the responses elicited by antigenic peptide and CT without IL-12. The dependence on IFNγ of mucosal and systemic CTL generation following IR immunization was demonstrated by the absence of such responses in mice which lack the ability to produce functional IFNγ, *e.g.*, as the result of a premature stop-codon in the IFNγ-encoding gene. The stop-codon mutation causes the gene to encode a truncated protein lacking the activity of IFNγ.

Kindly replace the paragraph at page 24, lines 7-21, with the following paragraph:

Accordingly, preferred formulations for administering soluble antigens and CTL-stimulatory cytokines within the methods of the invention are designed to optimize mucosal delivery. These agents may thus include [clyclodextrins] cyclodextrins and beta-cyclodextrin derivatives (*e.g.*, 2-hydroxypropyl-beta-cyclodextrin and heptakis(2,6-di-O-methyl-beta-cyclodextrin). These compounds, preferably conjugated with one or more of the active ingredients and formulated in an oleaginous base, are well documented to enhance bioavailability in intrarectal formulations. Other absorption-enhancing agents adapted for intrarectal delivery include medium-chain fatty acids, including mono- and diglycerides (*e.g.*, sodium caprate--extracts of coconut oil, Capmul), and triglycerides (*e.g.*, amylodextrin, Estaram 299, Miglyol 810).

Kindly replace the paragraph at page 39, lines 21-32, with the following paragraph:

Immunization Mice were immunized with 4 doses of the synthetic HIV peptide vaccine construct PCLUS3-18IIIB (Ahlers et al., J. Immunol. 150:5647-5665, (1993)) ([50©μg/mouse] for each immunization) (50μg/mouse for each immunization) on days 0, 7, 14 and 21 in combination with cholera toxin (CT) (10 μg/mouse) (List Biological Laboratories, Campbell, CA) by intrarectal administration. For subcutaneous immunization, incomplete Freund's adjuvant was used. rm IL,-12 (a generous gift of Genetics Institute, Inc., Cambridge, MA) was delivered either intraperitoneally (IP) (1μg) or intrarectally (1μg) mixed with DOTAP (Boehringer Mannheim), a cationic lipofection agent, along with the peptide vaccine.

Kindly replace the paragraph at page 48, lines 3-7, with the following paragraph:

One possible difference between CTL induced by mucosal versus systemic immunization is that the CTL resulting from the SC immunization do not have homing receptors for the GI mucosa, as evidenced by the fact that they are [note] not detected in the lamina propria or Peyer's patches.

IN THE CLAIMS:

6. (Amended) The method of claim [1] 5, wherein the cytokine is contacted with a mucosal surface of the subject.

27. (Amended) The method of claim [25] 26, wherein the cytokine is contacted with a mucosal surface of the subject.

48. (Amended) The immunogenic composition of claim 46, further comprising a base, carrier, or [aabsorption-promoting] absorption-promoting agent adapted for intrarectal delivery.

66. (Amended) The immunogenic composition of claim [66] 64, wherein the protein or peptide is an HIV V3 loop or T cell-binding peptide fragment thereof.